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Brain functional magnetic resonance imaging response to glucose and fructose infusions in humans

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Aims: In animals, intracerebroventricular glucose and fructose have opposing effects on appetite and weight regulation. In humans, functional brain magnetic resonance imaging (fMRI) studies during glucose ingestion or infusion have demonstrated suppression of hypothalamic signalling, but no studies have compared the effects of glucose and fructose. We therefore sought to determine if the brain response differed to glucose vs. fructose in humans independently of the ingestive process.

Methods: Nine healthy, normal weight subjects underwent blood oxygenation level dependent (BOLD) fMRI measurements during either intravenous (IV) glucose (0.3 mg/kg), fructose (0.3 mg/kg) or saline, administered over 2 min in a randomized, double-blind, crossover study. Blood was sampled every 5 min during a baseline period and following infusion for 60 min in total for glucose, fructose, lactate and insulin levels.

Results: No significant brain BOLD signal changes were detected in response to IV saline. BOLD signal in the cortical control areas increased during glucose infusion ($p = 0.002$), corresponding with increased plasma glucose and insulin levels. In contrast, BOLD signal decreased in the cortical control areas during fructose infusion ($p = 0.006$), corresponding with increases of plasma fructose and lactate. Neither glucose nor fructose infusions significantly altered BOLD signal in the hypothalamus.

Conclusion: In normal weight humans, cortical responses as assessed by BOLD fMRI to infused glucose are opposite to those of fructose. Differential brain responses to these sugars and their metabolites may provide insight into the neurologic basis for dysregulation of food intake during high dietary fructose intake.

Keywords: appetite control, glucose metabolism, neuropharmacology

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Introduction

Hypothalamic centres have been shown to control food intake and energy expenditure in response to changes in glucose levels [1]. Earlier work in this area focused on how hypoglycemia affects hypothalamic neuronal activity with subsequent elucidation of neuronal responses to changes in glucose levels that fall within the physiological range [1,2]. Two distinct populations of neurons in the hypothalamus have been described that respond oppositely to rising glucose levels: those that are glucose-inhibited (or glucose-sensitive) and decrease their activity, and those that are glucose-excited (or glucose-responsive) and increase their electrical firing rates [1,3]. In the ventromedial hypothalamus (VMH, including both the arcuate and ventromedial nuclei), it has been estimated that

~30% of the neurons respond to changes in glucose concentrations with approximately two-thirds that are glucose-excited and one-third that are glucose-inhibited [1,3]. Glucose-sensing neurons are also located in the lateral and paraventricular nuclei of the hypothalamus, which have extensive intra-nuclei connections between each other and the VMH [4]. These findings have led to current hypotheses that these glucose-sensing neurons in the hypothalamus play an integrating role in the brain's ability to maintain energy homeostasis [4–6].

Fructose is also another dietary carbohydrate with central effects that has been implicated in body weight regulation in animal models and humans [7–9]. The fructose-specific transporter, GLUT5, is found in microglia of the hippocampus and cortex [10] as well as Purkinje cells of the cerebellum [11], and the GLUT2 receptor, which has a low affinity for fructose, has been found in hypothalamic tanycytes [12]. A recent study in rodents demonstrated that an intracerebroventricular (ICV) injection of fructose had opposite effects to an injection of glucose on hypothalamic metabolism and food intake [13].

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Studying brain function in humans has been advanced by non-invasive neuroimaging technology. Functional brain magnetic resonance imaging (fMRI) is one such technique that detects changes in regional brain blood flow and concentrations of deoxygenated haemoglobin (abbreviated as blood oxygenation level dependent, or BOLD, signal) in response to a stimulus (i.e. viewing pictures, listening to sounds and performing a task) as a surrogate measure of neuronal activity [14,15]. Previous studies have explored the temporal response to glucose ingestion or infusion using fMRI and found suppression of hypothalamic BOLD signalling after administration of glucose to rats [16] and humans [17–20]. Obese subjects were found to have diminished attenuation of the BOLD signal suppression to glucose ingestion compared with lean subjects [21], and patients with type 2 diabetes have shown to show no hypothalamic signal change compared with non-diabetic patients [19]. No studies to date have, however, compared the brain BOLD response of glucose to fructose in humans. Thus, we hypothesized that the change in hypothalamic BOLD signal to glucose would be different from fructose in magnitude, direction or both. As study conditions, we chose to administer the carbohydrate boluses intravenously (IV) to avoid potentially confounding effects on the brain and hypothalamic BOLD response from neuronal responses to taste [22] or changes in levels of gut hormones [23], and included a control injection of saline.

Materials and Methods

Research Subjects

Nine healthy subjects (6 women, 3 men) with a mean \pm standard deviation age of 29 ± 4.3 years and body mass index of 22.0 ± 2.2 kg/m² were recruited using posted advertisements. Subjects were enrolled if they were at their maximal lifetime weight, had been weight stable for at least 3-months, were free of known medical illness, non-smokers, and not taking prescription medications and had no contraindication to exposure to strong magnetic fields. At the time of the screening visit, study participants met with a Bionutritionist of the Oregon Clinical and Translational Research Institute to review their current dietary intake. Subjects were enrolled if they were consuming a diet that approximated the typical American macronutrient intake (~35% of total calories as fat, 15% as protein and 50% as carbohydrates) and agreed to continue to do so during the duration of the study. Exclusionary criteria included abnormal renal or liver function tests, or elevated uric or lactic acid levels. The Oregon Health & Science University (OHSU) Investigational Review Board approved all procedures, and informed consent was obtained before study entry.

Study Design

Enrolled subjects returned on three separate visits to the OHSU Advanced Imaging Research Center. At each visit, following an overnight fast at approximately 8:00 A.M., an IV catheter was placed into a vein in each arm and subjects underwent a 60-min fMRI scan to measure BOLD response. This scan consisted of an initial baseline 10-min period after which an infusion of glucose (0.3 mg/kg), fructose (0.3 mg/kg) or saline was given

over 2 min. Typical infusion volumes using 50% concentration solutions for both glucose and fructose to administer roughly 20–25 g of carbohydrate typically ranged between 40 and 50 ml. Scanning continued during the infusion and for another 50 min. During the entire 60-min period, blood was collected every 5 min into heparinized tubes for separation of plasma and measurements of glucose and insulin (all three scans) and lactate (glucose and fructose scans only) and fructose (fructose scan only). The IV infusion and blood draws were performed by a nurse in the scanner suite. The scans were separated by at least 1 week and the infusion order was randomized.

Imaging Protocol

Images were acquired using a Siemens Magnetom Trio 3-Tesla (Siemens Medical Solutions, Malvern, PA, USA and Erlangen, Germany) whole body system. Subjects were positioned inside the bore of the magnet supine with their heads immobilized using cushions within a head coil. For each subject, T1-weighted three-dimensional high-resolution anatomic images (Sagittal MPRAGE repetition time: 2300 ms, echo time: 4.38 ms, flip angle: 12°, Slices: 144, FOV: 256 × 208, in-plane spatial resolution: 0.938 mm × 0.938 mm × 1 mm) were acquired for accurate anatomical localization of the hypothalamus (figure 1). Following this, a conventional T2-weighted gradient echo MRI pulse sequence was used for BOLD measurement (echo time: 32 ms; repetition time: 72 ms; flip angle: 20°; two contiguous mid-sagittal slices; FOV: 200; matrix 192 × 100; in-plane spatial resolution: 1 mm × 1 mm × 5 mm). These acquisition parameters were used to attempt to limit the artefact arising from the proximity of the hypothalamus to

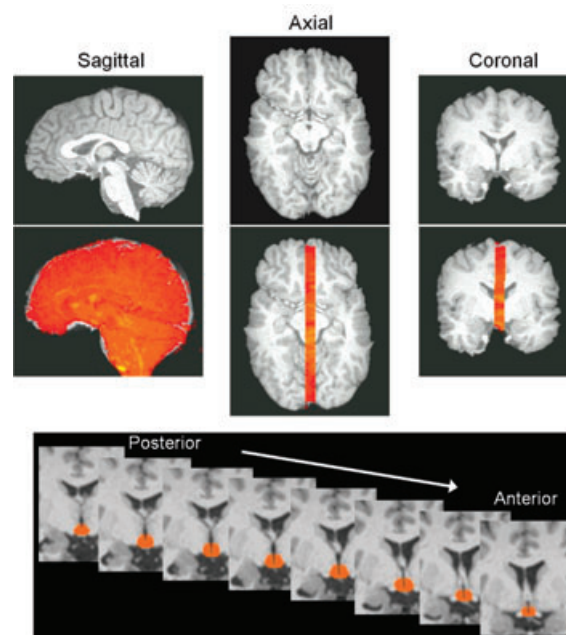


Figure 1. Upper panels: anatomic images depicting brain slice prescription for the functional data acquisition. Two slices (orange overlay) were acquired, each 1 × 1 × 5 mm on either side of midline. Lower panel: hypothalamic region of interest (ROI) (orange overlay) as hand drawn in a single subject.

the sinus cavity, which can introduce signal inhomogeneities into surrounding tissue. A total of 440 volumes were acquired during the 60-min scan.

Image Analysis

Following scan completion, all images underwent similar processing before analysis, including motion correction in two dimensions and linear detrending. The signal intensity was normalized using a *z*-score transformation, such that the average signal intensity was set equal to 0 and the standard deviation set equal to 1. Each functional scan was co-registered to the MPRAGE for anatomic localization and a single technician drew the hypothalamic region of interest (ROI) for comparison with the cortical control areas (figure 1) according to anatomic landmarks previously published [21]. Voxels that partially fell outside of the hypothalamus were manually removed before final analysis to reduce partial volume effects on the data. The hypothalamic ROI sizes for all subjects ranged between 110 and 176 voxels. Initially, the hypothalamus was separated into anterior and posterior, upper and lower segments [21], to determine if there were absolute or temporal differences in fMRI signal responses to the infusions in these regions. When no signal response differences were demonstrated, the regions were combined to increase power for final analysis. Each voxel time series was extracted and averaged on a voxel-wise basis. Initially, ten $10 \times 10 \text{ mm}^2$ cortical regions outside the hypothalamus were chosen for control areas, including the motor cortex as previously studied [17]. When all cortical sites demonstrated a similar BOLD response during each infusion, they were combined to form a non-hypothalamic cortical control region so as to increase statistical power. The baseline period was defined as the 5 min preceding IV infusion. Subsequent voxel time series were collapsed into 5-min bins for statistical comparisons of percent signal change from baseline in the hypothalamic ROI and cortical control areas.

Assays

Glucose, Insulin, and Lactate. Glucose and lactate were measured with a YSI Model 2300 analyser (Yellow Springs, OH, USA). Fasting plasma insulin concentrations were measured with a chemiluminescent immunoassay using the automated immulite system (Siemens Healthcare Diagnostics, Deerfield, IL, USA). This method has an analytical sensitivity of 13.9 pmol/l and an inter-assay COV of 6.4%.

Plasma Fructose. Plasma fructose concentrations were determined using a modification of a commercial glucose/fructose analytical kit (Megazyme, catalog item K-FRUGL; Xygen Diagnostics, Burgessville, Ontario, Canada) as previously described [24]. Reduced NADP (NADPH) absorbance was measured at 340 nm as a measure of sample glucose concentration (NADPH generation from glucose-6-phosphate reaction with G6PDH). Following this, phosphoglucose isomerase (PGI) was added to each well and NADPH absorbance was again measured (PGI converts fructose-6-phosphate to glucose-6-phosphate, with NADPH generation via G6PDH). The change

in absorbance from the previous reading was used to determine fructose concentration from a standard curve. To account for matrix effects, fructose standards were diluted in an EDTA-plasma matrix (plasma from overnight-fasted human subjects containing no detectable fructose).

Statistics

Glucose, fructose, insulin and lactate levels are reported as mean concentration \pm standard error of the mean, and paired *t*-tests were performed to determine statistical significance in concentration after infusion compared with baseline. Statistical significance was defined by two-tailed *p* value <0.05 . The observed haemodynamic signal changes in hypothalamus and control cortical areas were analysed separately using two-factor (3×9) repeated measures analysis of variance, with infusion (saline, fructose and glucose) and time (nine time bins) as the within-subjects factors. *Post hoc* comparisons were conducted using paired *t*-tests.

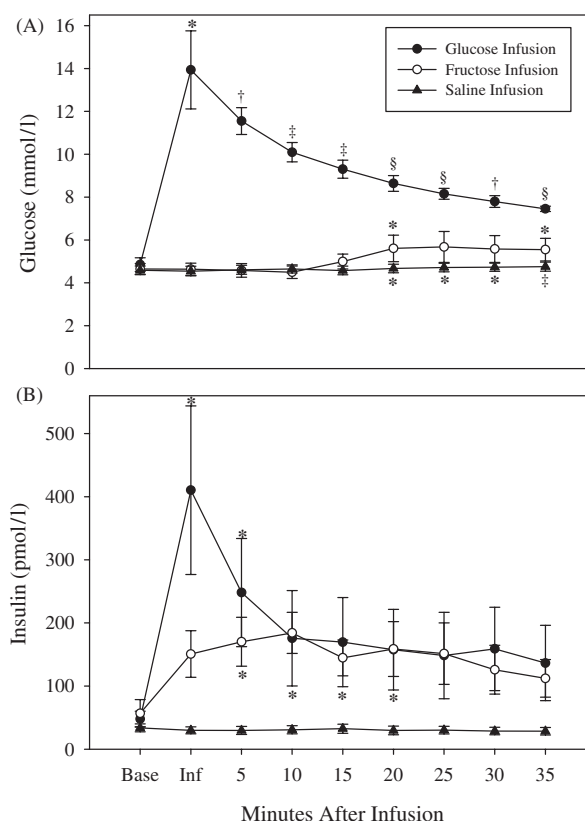


Figure 2. (A) Glucose levels and (B) insulin levels following infusion of glucose (closed circles), fructose scan (open circles) and saline scan (closed triangles) in normal weight adults. Base: 5-min baseline period. Inf: 5-min period including 2-min period of infusion. Results are mean \pm standard error. Glucose levels RMANOVA (glucose, fructose, saline): $F(2.7, 15.0) = 19.4$, $p < 0.001$. Insulin levels RMANOVA (glucose, fructose, saline): $F(3.9, 21.2) = 6.7$, $p = 0.001$. * $p < 0.05$, † $p < 0.001$, ‡ $p < 0.01$, § $p = 0.001$ compared with baseline by paired *t*-test.

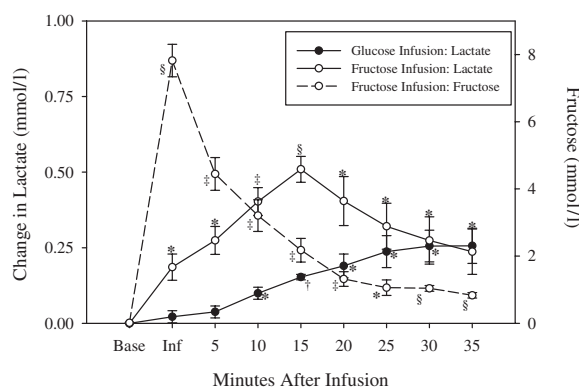


Figure 3. Levels of fructose and lactate following infusion of glucose and fructose in normal weight adults. Base: 5-min baseline period. Inf: 5-min period including 2-min period of infusion. Results are mean \pm standard error. Fructose levels $RMANOVA$ $F(8, 24) = 90.0$, $p < 0.001$. Lactate levels $RMANOVA$ (glucose, fructose) $F(8, 48) = 8.0$, $p < 0.001$. * $p < 0.05$, † $p < 0.001$, ‡ $p < 0.01$, § $p = 0.001$ compared with baseline by paired t -test.

Results

Plasma Glucose, Insulin, Fructose and Lactate Concentrations

During the saline infusion scans, plasma glucose and insulin concentrations remained close to baseline, although glucose levels drifted slightly upwards ($p < 0.05$) towards the end of the scanning period (figure 2). During the glucose infusion scans, both plasma glucose and insulin concentrations significantly increased, achieving peak levels of ~ 14 and ~ 400 pmol/l, respectively within the first 5 min (figure 2). Plasma lactate levels also increased progressively from baseline after a delay of ~ 10 min after the glucose infusion ($p < 0.05$ to < 0.01 compared with baseline; figure 3); whereas plasma insulin and glucose concentrations returned to baseline (figure 2). During the fructose infusion scans, plasma fructose levels increased in similar pattern as glucose did during the glucose infusion, from undetectable levels to a peak of ~ 8 mmol/l with in the first 5 min ($p < 0.05$ to < 0.001 compared with baseline; figure 3). Following the fructose infusion, plasma lactate levels significantly increased, peaking at 0.5 mmol/l 15 min after the infusion (figure 3) and glucose levels increased significantly ~ 20 – 25 min after the infusion ($p < 0.05$ compared with baseline; figure 2). Plasma insulin concentrations also increased ($p < 0.05$ compared with baseline) to ~ 150 pmol/l, beginning soon after the fructose infusion (figure 2) but remained substantially smaller than those observed after glucose infusion.

fMRI BOLD Signal Change in Response to Infusions of Saline, Glucose and Fructose

During the saline infusion, BOLD signal response across time in both the hypothalamus and brain cortical control regions did not vary significantly from baseline (figure 4). The BOLD responses in the cortical control regions differed significantly during the glucose, fructose and saline infusions [$F(4.3, 45.7) = 9.1$, $p < 0.001$] by three-way repeated measures analysis of variance (figure 4). In response to the glucose infusion, fMRI signal

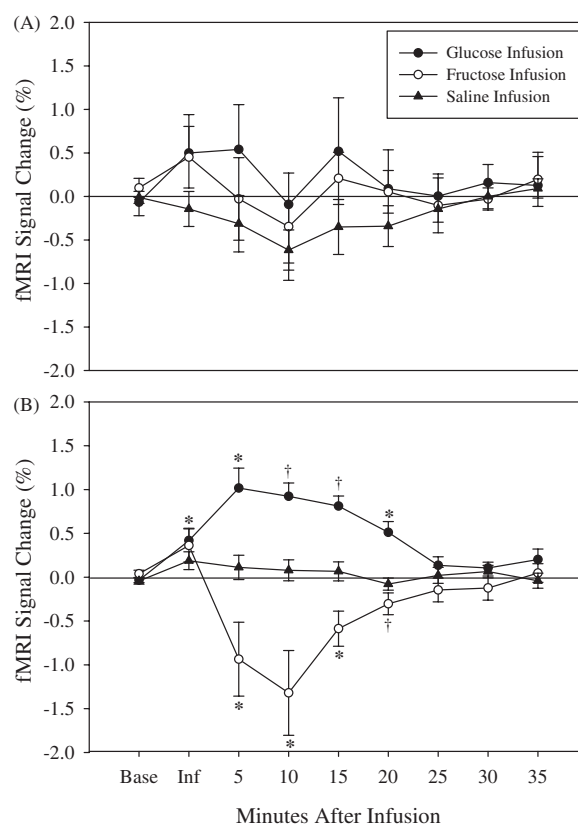


Figure 4. Percent functional magnetic resonance (fMRI) signal change in hypothalamus (A) and brain control regions (B) in response to a saline (closed triangles), glucose (closed boxes) and fructose infusions (open circles) in normal weight adults. Base: 5-min baseline period. Inf: 5-min period including 2-min period of infusion. Results are mean \pm standard error. $RMANOVA$ (glucose, fructose, saline): hypothalamus $F(6.4, 67.0) = 0.52$, $p = 0.80$, brain control regions [$F(4.3, 45.7) = 9.1$, $p < 0.001$]. * $p < 0.05$, † $p < 0.01$ compared with baseline by paired t -test.

in the cortical control regions increased significantly above baseline beginning with the infusion period and remained elevated for the next 20 min [$RMANOVA$ glucose vs. saline: $F(3.1, 40.8) = 5.6$, $p = 0.002$]. In contrast, during the fructose infusion BOLD signal decreased in the cortical control regions, also beginning shortly after infusion and remained depressed for 20 min [$RMANOVA$ fructose vs. saline: $F(1.8, 27.1) = 6.6$, $p = 0.006$]. The changes in BOLD signal in the hypothalamic ROI paralleled the cortical brain responses but did not achieve statistical significance at any binned period compared with baseline or when comparing between carbohydrate and saline infusions [three-way $RMANOVA$ $F(6.4, 67.0) = 0.52$, $p = 0.80$].

Safety

During the glucose infusion subjects most commonly reported a feeling of warmth, a 'sweet' taste in their mouth, or an urgency to urinate lasting only a few seconds. During the fructose infusions, subjects most commonly reported feeling cold, chest tightness or shortness of breath lasting a few minutes, but none noted a 'sweet' taste. No subject stopped their scan because of these effects. No blood lactate level exceeded 2.0 mmol/l during the fructose infusion, a predetermined safety cut-off level.

Discussion

We undertook the present studies to determine if changes in hypothalamic fMRI BOLD signal were different during a glucose infusion compared with a fructose infusion. Our study design included double-blind, randomized, crossover scanning sessions on different days that included an isovolemic infusion of saline as a control condition. We used a similar fMRI image acquisition method as previously published [17,21], including a narrow slice prescription through the midline to increase the sensitivity of detecting signalling changes in the hypothalamus. We further increased our sensitivity to detect hypothalamic BOLD signal changes by individually defining the hypothalamic ROI using each subject's anatomical scans and excluding non-brain regions from analysis.

Contrary to the expected reduction in hypothalamic BOLD signal based on previous glucose ingestion studies [17,21], we found that no significant changes in hypothalamic BOLD signal were detected during glucose infusion. Our finding is also in contrast to a recent study comparing hypothalamic BOLD response of oral to IV glucose by Smeets et al. in seven men [20]. In that study, which used a similar imaging protocol and hypothalamic anatomic landmarks to ours, the hypothalamic BOLD response to IV glucose was greatly attenuated (<1% difference compared with baseline) as compared to the suppression following glucose ingestion. Several notable differences between the studies, however, may explain these discrepant findings. In addition to studying a larger group of subjects that included both women and men, as opposed to just men, subjects in the present study also received a lower infusion dose of glucose (0.3 vs. 0.5 mg/kg). This dose was chosen because it is standard for insulin sensitivity testing [25], but may have resulted in further attenuation of the hypothalamic signal. On the other hand, it is unlikely that our data represent an absence of glucose responsiveness in the hypothalamus in humans. Rather, the hypothalamic BOLD signal during glucose could represent a confluence of both stimulatory and inhibitory neurons that, being in close proximity [1], cancelled each other out leading to a net signal change that was not significantly different from baseline. Alternatively, increases of circulating insulin and/or lactate concentrations, both of which have been shown to increase hypothalamic neuronal signalling [3], may have counteracted effects on predominantly glucose-inhibited neurons in this area. In any event, our data suggest that increases in levels of glucose and insulin are not the primary factors causing suppression of hypothalamic BOLD signal previously reported after glucose ingestion.

Comparison of BOLD response to IV fructose was undertaken because of recent studies linking high fructose consumption with weight gain, obesity and components of the metabolic syndrome [7–9,26]. Fructose given ICV to rats [7] and mice [13] increases food intake, an effect opposite to ICV glucose, which suppresses food intake. A high fructose diet increased body adiposity in mice [9], and studies in humans have shown that consumption of fructose-sweetened beverages increase subjective hunger ratings and *ad libitum* consumption of fat the following day [27]. Including an imaging session during an isovolemic, isocaloric fructose infusion also allowed us to compare the effects on BOLD response during IV glucose to

a similar osmotic load of another simple carbohydrate. Despite evidence for rapid uptake, metabolism and changes in cellular response to a site-specific hypothalamic injection of fructose in rodents [13,28], we found no significant change in hypothalamic BOLD signal change to IV fructose. Similar to the glucose infusion results, this finding could represent a composite signal generated by competing stimulatory effects, such as increases in peripheral and intrahypothalamic lactate levels [3,28] vs. potentially inhibitory effects mediated by induction of insulin resistance and reduced intra-neuronal insulin signalling [29], or as a result of the fact that fructose has a higher fractional extraction rate in the liver where initially higher concentrations could activate vagal afferents that might impact signalling in higher brain regions [30].

In contrast to the hypothalamic findings, we detected marked differences in cortical BOLD signal changes between the glucose and fructose infusion studies: a decrease during the fructose infusion compared with an increase during the glucose infusion. Although our subjects frequently experienced a flushing sensation during the glucose infusion, suggesting a vasodilatory response that might explain an increase in cortical BOLD signal, this sensation lasted only a few seconds on average (compared to the nearly 20 min sustained increase in cortical BOLD signal) and data from animal studies have shown that acute hyperglycemia or increased osmolality results in temporarily decreased, not increased, cerebral blood flow [31–33]. As for the net suppressive effect of fructose on cortical BOLD signal, this occurred despite the fact that fructose-specific receptors (GLUT5) are present in low concentrations throughout the brain [10,11,34], where the glucose transporter GLUT3 predominates [1]. Whether this cortical response to fructose is due to effects mediated by GLUT2 and GLUT5 carriers in the blood–brain barrier [34] or in local glia cells [10], due to increased osmolality [33], or is the indirect result of changes in levels of peripheral neural input or metabolic intermediaries which will require further study.

In summary, we found that glucose and fructose infusions in lower concentrations than previously given significantly stimulated and inhibited, respectively, net BOLD signal in cortical control regions but did not significantly alter hypothalamic BOLD signal. Frequent blood sampling during each infusion revealed appearances of additional hormones and metabolic products that could have contributed to these differential changes in the cortical signal, and potentially confounded the ability to detect significant signal changes in the hypothalamus. Nevertheless, the differences we report in brain responses to glucose and fructose infusions in these normal weight subjects are supportive of a neurological basis for the recently demonstrated effect of dietary fructose to promote weight gain in animals [9] and a preference for consumption of higher fat foods in humans [27].

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Conflict of Interest

J. Q. P., B. A. K., A. A. S., C. K. and W. D. R. helped in designing the study and conduct/data collection. J. Q. P., B. A. K., P. J. H., S. H. A., T. N. D., C. K. and W. D. R. analysed the study. J. Q. P., B. A. K., A. A. S., P. J. H., S. H. A., T. N. D., C. K. and W. D. R. wrote the manuscript.

No author has competing interests or disclosures.

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